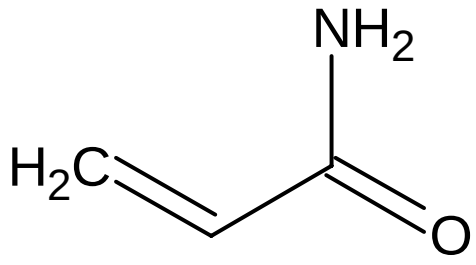
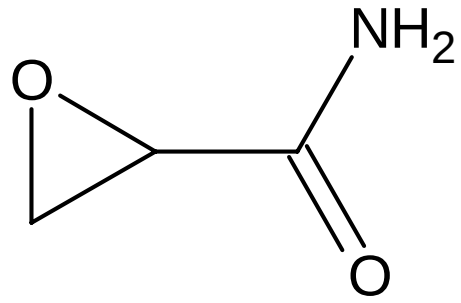
Acrylamide--Risk Assessment Overview

- Structure and metabolic activation via an epoxide are analogous to vinyl chloride, and create a strong presumption of genetically-mediated carcinogenic activity.
- Recent *in vivo* observations in mice indicate linear or slightly supralinear dose response over a wide range of dosage for a chromosome-breakage type genetic activity [micronuclei--Abramsson-Zetterberg (2003) Mutat Res. 535(2):215-22].
- Animal bioassay data are extensive, consistent, and superior to most data sets that have been the basis of Proposition 65 qualitative and quantitative determinations. (Clear evidence in two drinking water studies in rats for multiple sites; supportive data in mice).
- There is reason for enhanced concern for early life exposures to mutagenic carcinogens, based on recent analyses of generic animal bioassay evidence for other compounds. There is also evidence that young children have greater average dietary exposures to acrylamide than adults.
- Human epidemiological data are not inconsistent with quantitative risk projections from the animal studies.
- More modern quantitative risk assessment approaches will allow OEHHA to provide the public with improved insights into acrylamide's dietary risks; and encourage prudent incremental reductions in exposures.

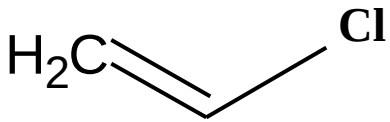
acrylamide



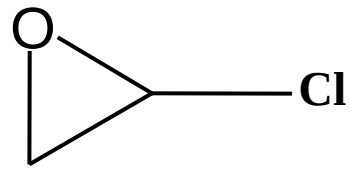
glycidamide



vinyl chloride



chloroethylene oxide



Tumors in female F344 rats receiving acrylamide in drinking water for 104 weeks (Johnson *et al.*, 1986)

Tissue/tumor	**Acrylamide, mg/kg-day**					
	Control	**0.01**	**0.1**	**0.5**	**1.0**	**trend**
Mammary gland						
adenocarcinoma	2/60	1/60	1/60	2/58	6/61	p=0.0071
benign	10/60	11/60	9/60	19/58[b]	23/61[b]	p=0.0002
CNS, glial tumor	1/60	2/59	1/60	1/60	9/61[b]	p=0.0002
Thyroid gland						
follicular cell adenoma or adenocarcinomas	1/58	0/59	1/59	1/58	5/60[b]	p=0.0028
Oral cavity						
SC papilloma or carcinoma[a]	0/60	3/60	2/60	3/60	8/61[b]	p=0.0013
Uterus						
adenocarcinoma	1/60	2/60	1/60	0/59	5/60[b]	p=0.03
Clitoral gland						
adenoma or carcinoma[a]	0/60	1/60	3/60	4/59	5/59[b]	p=0.01

[a] Assumes primary benign and malignant tumors did not occur in the same animal.

[b] $p \leq 0.05$

Tumors in female F344 rats receiving acrylamide in drinking water for 104 weeks (Friedman *et al.*, 1995)

Tissue	Acrylamide, mg/kg-day			
	Control[a]	1.0	3.0	(trend)[f]
Mammary gland adenocarcinoma, adenoma, fibroma or fibroadenoma	14/96	21/94	30/95[b]	p=0.0028
Central Nervous system glial tumor	0/99	2/100	3/90	p=0.10
Thyroid gland FC adenoma or adenocarcinoma	1/100	10/100[b]	23/100[b]	p<0.0001

[a] Two concurrent control groups were combined. Tumor rates observed in both control groups were similar.

[b] $p \leq 0.05$

Tumors in female F344 rats receiving acrylamide in drinking water for 104 weeks (Friedman et al., 1995)

Tissue	Acrylamide, mg/kg-day			
	Controls	1.0	3.0	trend
Mammary Gland				
adenocarcinoma adenoma, fibroma or fibroadenoma	11/96	21/94	30/95	p=0.0028
Central Nervous System glial tumor	0/99	2/100	3/100	p=0.06
Thyroid gland FC adenoma or adenocarcinoma	1/100	10/100	23/100	p<0.0001

Tumors in male F344 rats receiving acrylamide in drinking water for 104 weeks (Friedman et al., 1995)

Tissue	Acrylamide, mg/kg-day				
	Controls	0.1	0.5	2.0	trend
Central Nervous System					
glial tumor	2/204	2/98	1/50	3/75	p=.06
Thyroid gland					
FC adenoma or	6/202	12/203	5/101	17/75	p<0.000
adenocarcinoma					
Testis					
Tunic-mesothelioma	8/204	9/204	8/102	13/75	p<0.000

Recent Analysis of Life-Stage Differences in Susceptibility (Relative to Adults) for Carcinogenesis from Mutagenic Carcinogens Given in Continuous Dosing Protocols

(5 chemicals, 51 tumor incidence observations)

	Maximum likelihood estimate of cancer inductions per dose/(body weight$^{.75}$ -day) relative to comparably dosed adults	**95% LCL**	**95% UCL**
Fetal	7.8	4.3	13.1
Birth-Weaning	20	14.7	28
Weaning-60 days	4.5	0.49	10.0

Recent Analysis of Life-Stage Differences in Susceptibility (Relative to Adults) for Carcinogenesis from Mutagenic Carcinogens Given in Discrete (1-4X) Dosing Protocols

(6 chemicals, 274 tumor incidence observations in animal groups)

	Maximum likelihood estimate of cancer inductions per dose/(body weight$^{.75}$ -day) relative to comparably dosed adults	**95% LCL**	**95% UCL**
Fetal Period (8 days beginning GD 12)	5.1	3.6	8.5
Birth-Weaning (21 days)	10.5	7.2	16.2
Weaning-60 days (39 days)	1.51	1.03	2.3

FDA Estimates of Current U.S. Dietary Intakes of Acrylamide

(Data Source: Robie D. and DiNovi M. presentation 2/24/03)

Daily mean intake estimates in µg/kg BW-day

Source of food consumption data	All 2+ Years	2-5 Year Olds	Ratio 2-5's/total 2+
MRCA 1982-7	0.48	1.26	2.63
CSFII 1989-92	0.32	0.78	2.44
CSFII 1994-96, 1998	0.37	1.00	2.70

Daily mean intake in µg/kg BW^.75 -day

	All 2+ Years	2-5 Year Olds	Ratio 2-5's/total 2+
MRCA 1982-7	1.37	2.55	1.86
CSFII 1989-92	0.91	1.58	1.73
CSFII 1994-96, 1998	1.06	2.03	1.92

Comments on Public Reports of the Mucci et al. (2003) Case Control Epidemiological Study

- **"This study provides some evidence that the amount of acrylamide people are taking in is probably not sufficient to increase the risk of cancer."**

- **By not including the word "detectably" before "increase" this statement fails to fairly warn the reader of the problem of statistical insensitivities in this and any other epidemiological study. There could well be increases in cancer rates that are of great social significance but well below the amount of increase that would show up as a sufficiently elevated level to have been considered "statistically significant" by conventional criteria. The confidence limits in Table 4 of Dr. Mucci's paper indicated that in order to be detected statistically, people classified in the highest quarter of estimated acrylamide exposures would have had to had approximately 40% - 70% greater risks for the three cancers than people classified in the lowest quarter.**

Thrust of the Boston Globe Story--acrylamide "may not be as dangerous as people have been led to believe."

- **Unfortunately implies the Mucci study contains a disciplined comparison with the human cancer risks that have been projected from available long term cancer studies at higher levels of acrylamide exposure in animal.**
- **(These projections led the original Swedish researchers to project population aggregate risks of hundreds of cases per year in Sweden, and we followed up with projections of thousands of extra cancer cases per year in the U.S. based on estimates of U.S. dietary acrylamide intakes.) The Mucci study makes no quantitative comparison of what they observed with what would be expected for the relative risks in the populations they studied.**

"These data suggest the doses of acrylamide people are taking in can be effectively detoxified."

- **The Mucci paper also does not contain any detailed review and analysis of available pharmacokinetic data for acrylamide. The available hemoglobin adduct data in humans not exposed via smoking or occupational sources indicates that appreciable amounts of acrylamide and its DNA reactive metabolite escape detoxification for substantial periods in the body and there should be no expectation that dietary exposure levels are fully detoxified before they can induce the mutations that can contribute to the molecular pathological pathways of cancer in people.**

My Conclusion

- **In my view, it would be tragic if the scientific overreaching that appears in the press reports of Dr. Mucci's paper were to mislead people in the food processing industry and relevant governmental authorities to slacken their search for ways to prudently reduce human exposures to this widespread genetically active carcinogen in food**.

Toward an Improved Distributional Risk Assessment for Acrylamide

- Use of animal cancer observations from both sexes (Johnson et al., 1986)) and an additional more recent experiment in rats (Friedman et al., 1995)
- Consideration of cancer bioassay results, mutagenicity, and hemoglobin adduct formation in mice, compared to rats (Pausson et al., 2002; Segerback et al., 1995; Sumner et al., 1992; Bull et al., 1984ab; Robinson et al, 1986),
- A more advanced distributional analysis to represent uncertainties in the projection of the cancer potency for average humans in relation to potencies observed in available animal bioassays (Hattis et al., 2002),
- PBPK models and measurements of hemoglobin adduct formation in humans to estimate internal doses of acrylamide and its metabolite in people in relation to external dose for better comparison with the cancer observations in relation to internal doses in the rats,

Toward an Improved Distributional Risk Assessment for Acrylamide, Cont.

- Explicit accounting for the likely increased exposures and sensitivity of children.
- Explict accounting for the likely interindividual variability in sensitivity for carcinogenesis in people.
- Consideration of alternative ways of modeling acrylamide risks, such as the multiplicative relative risk approach recommended by Swedish researchers by analogy with radiation cancer risk projections.
- Bayesian updating of projected human risks using limited available epidemiological observations from occupational groups exposed to acrylamide via inhalation and dermal routes.
- **All things considered, it should not be expected that these improvements will lead to net changes in estimated acrylamide dietary cancer risks by more than several fold in either direction.**